Amendments to the Specification

Please add a paragraph beginning at page 1, after the title with the following paragraph:

Cross Reference to Related Applications

_____ This is a § 371 U.S. national stage of PCT/GB2004/002827, filed June 28, 2004, which was published in English under PCT Article 2(2), and claims the benefit of Great Britain application 0315182.6, filed June 28, 2003. Both applications are incorporated herein in their entirety._

Please replace the paragraph beginning at page 19, line 8, with the following rewritten paragraph:

Figure 1 shows the amino acid sequence of human GH (SEQ ID NO: 9) with binding site for GHR indicated with arrows;

Please replace the paragraph beginning at page 19, line 11 with the following rewritten paragraph:

Figure 2 shows the nucleic acid sequence of human GH (SEQ ID NO: 10);

Please replace the paragraph beginning at page 19, line 13 with the following rewritten paragraph:

Figure 3 shows the amino acid sequence of GHR (SEQ ID NO: 11) (extracellular domain underlined);

Please replace the paragraph beginning at page 19, line 15 with the following rewritten paragraph:

Figure 4 Cloning strategy for the circular permutation of Growth Hormone. In the first PCR reaction a forward primer (GH_CPFor (SEQ ID NO: 13)) and a linker primer (GH_CPLink (SEQ ID NO: 14)) are used to produce a 'megaprimer'. This megaprimer is used with a reverse primer (GH_CPRev (SEQ ID NO: 15)) to generate the circularly permutated GH gene. Appropriate restriction sites [*Bam*HI (B) and *Not*I (N)] are engineered into the forward and reverse primers to facilitate ligation into the vector pTrcHis-TOPO;

Please replace the paragraph beginning at page 19, line 22 with the following rewritten paragraph:

Figure 5: Schematic and DNA sequence showing the strategy used to generate GH_CP01 (SEQ ID NO: 12). (A) a schematic diagram showing how GH is transformed into GH_CP01 (SEQ ID NO: 12); Glu120 (grey disc) is removed by initiating the new gene at residue 121 and terminating the protein at residue 118, the 'old' termini are linked by joining the termini to make a 6 amino acid linker. The helices are numbered in order (from N to C terminus) and the arrows denote the direction of the helices (from N to C). (B) the DNA sequence of GH and GH_CP01 (SEQ ID NO: 12); the nucleotides removed from GH to produce GH_CP01 (SEQ ID NO: 12) are underlined, the initiation nucleotide for GH_CP01 (SEQ ID NO: 12) in GH, and *vice versa*, are shown in bold;

Please replace the paragraph beginning at page 20, line 16 with the following rewritten paragraph:

Table 1 Primers used to generate GH_CP01 (GH_CP01For (SEQ ID NO: 13), GH_CP01Rev (SEQ ID NO: 15)). The bold characters denote sequence which anneals to the GH gene; the underlined characters denote endonuclease restriction sites (*Bam*HI – ggatcc; *Not*I – gcggccgc). In the linker primer, GH_CP01Link (SEQ ID NO: 14), the sequence which anneals to the carboxy terminus of GH is shown in UPPER-CASE.

Please replace the paragraph beginning at page 20, line 22 with the following rewritten paragraph:

Table 2 Primers used to generate further circularly permuted GH molecules. GHPermL01+ is put forth as SEQ ID NO: 16, GHPermL01- is put forth as SEQ ID NO: 17 GHPermN01+ is put forth

as SEQ ID NO: 18 GHPermC01- is put forth as SEQ ID NO: 19 GHPermN01+ is put forth as
SEQ ID NO: 20 GHPermC02- is put forth as SEQ ID NO: 21 GHPermN01+ is put forth as SEQ
ID NO: 22 GHPermN04+ is put forth as SEQ ID NO: 24 GHPermC01- is put forth as SEQ ID
NO: 25 GHPermN04+ is put forth as SEQ ID NO: 26, GHPermC02- is put forth as SEQ ID NO:
27, GHPermN06+ is put forth as SEQ ID NO: 28, GHPermC06- is put forth as SEQ ID NO: 29,
GHPermN07+ is put forth as SEQ ID NO: 30, GHPermC07- is put forth as SEQ ID NO: 31.

*Please replace the paragraph beginning at page 24, line 3 with the following rewritten
paragraph:*

IQTLMGRLED GSPRTGQIFK QTYSKFDTNS HNDDALLKNY GLLYCFRKDM DKVETFLRIV
QCRSVEGSTI PLSRLFDNAS LRAHRLHQLA FDTYQEFEEA YIPKEQKYSF LQNPQTSLCF
SESIPTPSNR EETQQKSNLE LLRISLLLIQ SWLEPVQFLR SVFANSLVYG   ASDSNVYDLL
KDLE (SEQ ID NO: 1)

*Please replace the paragraph beginning at page 24, line 16 with the following rewritten
paragraph:*

```
1                                                    GAGGACTTAAATTAAATA
    Met Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly    17
 19 ATG ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG GGA

    Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp    34
 70 CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC GAC

    Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met    51
121 GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT ATG

    Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly    68
172 GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG GGC

    Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His    85
223 TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA CAC

    Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr   102
274 AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG TAT

    Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu   119
325 ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG CTG

    Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln   136
376 TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG CAG

    Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp   153
427 AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC TGG

    Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr   170
```

```
478 TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT TAT
    Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Stop      185
529 GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC GAA TAA   (SEQ ID NO : 2)
```

Please replace the paragraph beginning at page 25, line 5 with the following rewritten paragraph:

```
MEIQTLMGRL  EDGSPRTGQI  FKQTYSKFDT  NSHNDDALLK  NYGLLYCFRK
DMDKVETFLR  IVQCRSVEGS  TIPLSRLFDN  ASLRAHRLHQ  LAFDTYQEFE
EAYIPKEQKY  SFLQNPQTSL  CFSESIPTPS  NREETQQKSN  LELLRISLLL
IQSWLEPVQF  LRSVFANSLV  YGASDSNVYD  LLKDL  (SEQ ID NO : 3)
```

Please replace the paragraph beginning at page 25, line 13 with the following rewritten paragraph:

```
  1                                          GAGGACTTAAATTAAATA
    Met Glu Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr    17
 19 ATG GAA ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG

    Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn    34
 70 GGA CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC

    Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp    51
121 GAC GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT

    Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu    68
172 ATG GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG

    Gly Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala    85
223 GGC TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA

    His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala   102
274 CAC AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG

    Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser   119
325 TAT ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG

    Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln   136
376 CTG TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG

    Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser   153
427 CAG AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC

    Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val   170
478 TGG TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT

    Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Stop      185
529 TAT GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC TAA (SEQ ID NO : 4)
```

Please replace the paragraph beginning at page 25, line 54 with the following rewritten paragraph:

```
MQTLMGRLED   GSPRTGQIFK   QTYSKFDTNS   HNDDALLKNY   GLLYCFRKDM   DKVETFLRIV

QCRSVEGSTI   PLSRLFDNAS   LRAHRLHQLA   FDTYQEFEEA   YIPKEQKYSF   LQNPQTSLCF

SESIPTPSNR   EETQQKSNLE   LLRISLLLIQ   SWLEPVQFLR   SVFANSLVYG   ASDSNVYDLL

KDLE (SEQ ID NO : 5)
```

Please replace the paragraph beginning at page 26, line 4 with the following rewritten paragraph:

```
1                                                    GAGGACTTAAATTAAATA
      Met Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln      17
   19 ATG CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG GGA CAA

      Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp      34
   70 ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC GAC GAT

      Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp      51
  121 GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT ATG GAT

      Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser      68
  172 AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG GGC TCC

      Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His Arg      85
  223 ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA CAC AGA

      Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile     102
  274 TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG TAT ATT

      Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys     119
  325 CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG CTG TGC

      Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys     136
  376 TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG CAG AAA

      Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp Leu     153
  427 TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC TGG TTG

      Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr Gly     170
  478 GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT TAT GGG

      Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Stop           184
  529 GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC GAA TAA (SEQ ID NO : 6)
```

Please replace the paragraph beginning at page 26, line 45 with the following rewritten paragraph:

MC̲IQTLMGRL EDGSPRTGQI FKQTYSKFDT NSHNDDALLK NYGLLYCFRK

DMDKVETFLR IVQCRSVEGS TIPLSRLFDN ASLRAHRLHQ LAFDTYQEFE

EAYIPKEQKY SFLQNPQTSL CFSESIPTPS NREETQQKSN LELLRISLLL

IQSWLEPVQF LRSVFANSLV YGASDSNVYD LLKDLEC̲   (SEQ ID NO : 7)

Please replace the paragraph beginning at page 26, line 54 with the following rewritten paragraph:

```
  1                                              GAGGACTTAAATTAAATA
     Met Cys Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr   17
  19 ATG TGT ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG
     Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn   34
  70 GGA CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC
     Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp   51
 121 GAC GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT
     Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu   68
 172 ATG GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG
     Gly Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala   85
 223 GGC TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA
     His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala  102
 274 CAC AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG
     Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser  119
 325 TAT ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG
     Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln  136
 376 CTG TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG
     Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser  153
 427 CAG AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC
     Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val  170
 478 TGG TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT
     Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Cys  187
 529 TAT GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC GAA TGT
     Stop                                                                  187
 580 TAA   (SEQ ID NO : 8)
```

Please insert the attached Abstract as the last page of the specification.